REMARKS

Status of Claims

Claims 1-21, 23-27, and 29-76 are currently pending. Claim 68 has been amended. Claims 11-14, 24, 29, 32-34, 50, and 54-62 are withdrawn. Support for the amended claims is found throughout the specification as originally filed. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

Claims 22 and 28 have been canceled without prejudice or disclaimer as to the claimed subject matter solely to expedite prosecution of the present application. Applicants reserve the right to pursue canceled subject matter in one or more continuation or divisional applications, as appropriate.

Reply to Claim Rejections under 35 U.S.C. § 112, second ¶

Claims 22 and 28 are rejected under 35 U.S.C. § 112, second ¶ as allegedly being indefinite. This rejection is moot as claims 22 and 28 are canceled. Accordingly, Applicants respectfully request withdrawal of these rejections.

Claims 68-71 are rejected under 35 U.S.C. § 112, second ¶ as allegedly being indefinite. Applicants respectfully submit that the present amendment to claim 68 address the issues raised by the Examiner. Accordingly, Applicants respectfully request withdrawal of these rejections.

Reply to Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pickar *et al.* (U.S. Patent No. 5,492,907) in view of Beasley, Jr. *et al.* (U.S. Patent No. 5,605,897). In setting forth the rejection, the Examiner asserts that "[i]t would have been obvious to one of ordinary skill in the art to incorporate the D2 dopamine receptor antagonist of Beasley Jr. *et al.* into the

invention of Pickar *et al.* because Pickar teaches the use of a D2 dopamine receptor antagonist in a pharmaceutical formulation used to treat serious psychotic mental illness and Beasley Jr. *et al.* teaches that the D2 dopamine receptor antagonist, olanzipine, used in treating disorders of the central nervous system." See the Office Action at page 5. Applicants respectfully submit that the reasons of obviousness set forth by in the Office Action are flawed for the reasons below.

Pickar *et al.* discloses the combination a typical antipsychotic drug with an α_2-adrenergic receptor antagonist. The "typical" antipsychotic drugs disclosed in Pickar *et al.* have the general mechanism of action of D_2 dopamine receptor antagonism. "Atypical" antipsychotics differ from conventional antipsychotics in their pharmacological profiles. While typical antipsychotics are characterized principally by D_2 dopamine receptor blockade, atypical antipsychotics show antagonist effects on multiple receptors including the $5HT_{2a}$ and $5HT_{2c}$ serotonin receptors and varying degrees of receptor affinities. Accordingly, atypical antipsychotic drugs are commonly referred to as serotonin/dopamine antagonists.

Because of their differing pharmacological profiles one of ordinary skill in the art would not expect that these classes of drugs are fungible in combination therapies. Specifically, while Pickar *et al.* discloses the combination a typical antipsychotic drug with an α_2-adrenergic receptor antagonist provides a drug treatment regimen with a desirable side effect profile, one of ordinary skill in the art would not have expected that the combination of an atypical antipsychotic drug with an α_2-adrenergic receptor antagonist would produce the same results. Indeed, the atypical antipsychotic clozapine differs in that it possess an affinity for the α_2-adrenergic receptor that exceeds its affinity for the D_2 receptor. This property is unique to clozapine among the other members of the atypical antipsychotic class. Clozapine is also associated with severe side effects, which also distinguishes clozapine from other atypical antipsychotics. Given the above experience with clozapine, one of ordinary skill in the art would have expected that the combination of atypical antipsychotic drug with an α_2-adrenergic receptor antagonist, as is now claimed, would lead to a drug regimen that would produce the same or similar undesirable side effect profile that is experienced with clozapine.

The present application, however, discloses the unexpected results that an atypical antipsychotic drug may be combined with an α_2-adrenergic receptor antagonist without the undesirable side effects. As set forth in KSR Int'l Co. v. Teleflex Inc., "combining elements that work together 'in an unexpected and fruitful manner' would not have been obvious." 127 S. Ct. 1727, 1740 (2007). The present claims are directed to the combination of an atypical antipsychotic drug with an α_2-adrenergic receptor antagonist produces both an unexpected and fruitful result. Example 1 of the specification shows that adjunctive treatment with a selective α_2 adrenergic receptor antagonist (idazoxan) to relatively low doses of an atypical antipsychotic with low affinity for α_2 adrenergic receptors (olanzapine) produced a significant antipsychotic-like effect without catalepsy. The present results, obtained by a combination of idazoxan and olanzapine, demonstrate an equally or more effective suppression of the CAR by the use of only 2.5 mg/kg of olanzapine. Thus, these data indicate that the dose of olanzapine required to obtain an effective antipsychotic effect may be reduced by almost 50% through the adjunct treatment with idazoxan. These results are truly unexpected as explained above.

In view of the above, Applicants respectfully submit that a one of ordinary skill in the art would not have expected that the combination of an atypical antipsychotic drug with an α_2-adrenergic receptor antagonist to result in a desirable treatment regimen, and therefore, the method set forth in the present claim would not have been obvious. Accordingly, Applicants respectfully request withdrawal of this rejection.

Reply to Double Patenting Rejection over U.S. Patent No. 5,492,907

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Pickar *et al.* (U.S. Patent No. 5,492,907) in view of Beasley, Jr. *et al.* (U.S. Patent No. 5,605,897). Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the subject matter claimed in a commonly owned patent. See MPEP § 804(II)(B)(1)(emphasis in original). Further, a double patenting rejection of the obviousness-type, is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally

underlying the double patenting rejection is not considered prior art. MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967).

This rejection sets forth the same rationale for combining these references as was set forth in the 35 U.S.C. § 103(a) rejection. As presented above, however, Applicants respectfully submit that a one of ordinary skill in the art would not have expected that the combination of an atypical antipsychotic drug with an α_2-adrenergic receptor antagonist to result in a desirable treatment regimen, and therefore, the method set forth in the present claim would not have been obvious. Further, the claims of the present application are patentably distinct from the claims of U.S. Patent No. 5,492,907. Accordingly, Applicants respectfully request withdrawal of this rejection.

Reply to Double Patenting Rejection over U.S. Patent No. 5,663,167

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6 and 7 of Pickar *et al.* (U.S. Patent No. 5,663,167) in view of Beasley, Jr. *et al.* (U.S. Patent No. 5,605,897). U.S. Patent No. 5,663,167 is related to U.S. Patent No. 5,492,907 cited in the above double patenting rejection. As with U.S. Patent No. 5,492,907, U.S. Patent No. 5,663,167 discloses the combination a typical antipsychotic drug with an α_2-adrenergic receptor antagonist. In combining U.S. Patent No. 5,663,167 with Beasley, Jr. *et al.*, the Office Action uses the same rationale for combining these references as was set forth in the 35 U.S.C. § 103(a) rejection combining U.S. Patent No. 5,492,907 with Beasley, Jr. *et al.*. As presented above, however, Applicants respectfully submit that a one of ordinary skill in the art would not have expected that the combination of an atypical antipsychotic drug with an α_2-adrenergic receptor antagonist to result in a desirable treatment regimen, and therefore, the method set forth in the present claim would not have been obvious. Further, the claims of the present application are patentably distinct from the claims of U.S. Patent No. 5,663,167. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

It is believed that no additional fees are required with this submission. However, in the event that additional fees are deemed necessary, or in the event of any variance between the amount enclosed and the fees determined by the USPTO, please charge or credit any such variance to the undersigned's Deposit Account No. 50-0311, Reference No. 26811-010 UTIL.

Respectfully submitted,

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